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Liposome Bupivacaine Femoral Nerve Block for Postsurgical Analgesia after Total Knee Arthroplasty

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ABSTRACT

Background: The authors evaluated the efficacy of liposome bupivacaine in a femoral nerve block (FNB) after total knee arthroplasty.

Methods: Part 1: subjects received FNB with 20 ml liposome bupivacaine (67, 133, or 266 mg) or placebo. Part 2: subjects were randomized to FNB with liposome bupivacaine 266 mg or placebo. The primary outcome measure was area under the curve of the numeric rating scale score for pain intensity at rest through 72 h (AUC NRS-$R_{0–72}$) with imputed scores after rescue medication.

Results: In part 1, FNB with liposome bupivacaine 266 mg (n = 24) resulted in analgesia similar to that obtained with 133 mg and was chosen for part 2. In part 2, least-squares mean (standard error) AUC NRS-$R_{0–72}$ was lower with liposome bupivacaine 266 mg (n = 92) than with placebo (n = 91; 419 [17] *vs.* 516 [17]; $P < 0.0001$). This outcome remained unchanged in a *post hoc* analysis without score imputation (221 [12] *vs.* 282 [12]; $P = 0.0005$). Least-squares mean AUC NRS-R with imputed scores was lower with liposome bupivacaine during each 24-h interval (0 to 24, 24 to 48, and 48 to 72 h) after surgery; AUC NRS-R without imputed scores was lower during the 0- to 24-h and 24- to 48-h intervals. The liposome bupivacaine group had lower mean total opioid use (76 *vs.* 103 mg morphine; $P = 0.0016$). Pain was sufficiently severe to require second-step rescue with opioids *via* intravenously administered patient-controlled analgesia in 92% of liposome bupivacaine patients and 81% of placebo patients. With patient-controlled analgesia and other forms of rescue analgesia, mean NRS scores with activity were moderate in both liposome bupivacaine and placebo groups throughout the part 2 study period. Incidence of adverse events was similar between the groups (part 1: 90 *vs.* 96%; part 2: 96 *vs.* 96%, respectively).

Conclusion: FNB with liposome bupivacaine (266 mg) resulted in modestly lower pain scores and reduced opioid requirements after surgery, with an adverse event profile similar to placebo. **(ANESTHESIOLOGY 2016; 124:1372-83)**

PATIENTS undergoing total knee arthroplasty (TKA) typically experience moderate to severe postsurgical pain[1–3] that can last for several days. Effective pain management facilitates early ambulation and rehabilitation,[4,5] which in turn hastens recovery, reduces length of stay, and decreases patient risk for complications including thromboembolism and nosocomial infection.[6] Use of femoral nerve block improves postsurgical analgesia and reduces parenteral opioid requirements in patients undergoing TKA.[1,6–10] However, single-injection femoral nerve blocks are limited by the relatively short duration of analgesia provided by the currently available formulations of local anesthetics (typically 24 h or less).[6,11] Duration of analgesia can be prolonged with

What We Already Know about This Topic

- Liposome bupivacaine is approved for administration into the surgical site but not for peripheral nerve blocks

What This Article Tells Us That Is New

- In a two-part clinical study designed to meet the U.S. Food and Drug Administration standard for approval of analgesic agents, femoral nerve block with liposome bupivacaine after total knee arthroplasty resulted in modestly reduced average pain and opioid use in the first 72 h after surgery compared with placebo
- Side effects were similar in both groups, supporting further investigation

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continuous peripheral nerve blocks. However, this requires placement of a perineural catheter,[11,12] continuous infusion of local anesthetic, inconvenience of carrying catheter and local anesthetic reservoir/pump, infusion management and catheter site care, infection, leakage, accidental dislocation, and cost and maintenance of equipment.[11,13]

Liposome bupivacaine (bupivacaine liposome injectable suspension; EXPAREL®; Pacira Pharmaceuticals, Inc., USA) is a multivesicular formulation of bupivacaine indicated for administration into the surgical site to produce postsurgical analgesia.[14] Liposome bupivacaine has been shown to provide postsurgical analgesia across a range of surgical models, with a safety profile that is similar to that of bupivacaine HCl.[15–17] While available data in volunteers suggest that liposome bupivacaine in a femoral nerve block results in prolonged blockade,[18] its analgesic effects when used in a peripheral nerve block in a setting of acute postsurgical pain remain unknown.

Materials and Methods

Study Overview

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study designed to meet the U.S. Food and Drug Administration (FDA) standard for approval of analgesic agents, which rests on comparison of investigational agents *versus* placebo in well-matched populations. The objective was to assess efficacy, safety, and pharmacokinetics of liposome bupivacaine when administered as a single injection in a femoral nerve block in subjects undergoing primary unilateral TKA under general, spinal, or epidural anesthesia (Study Director: Erol Onel, M.D.; U.S. National Institutes of Health [www.clinicaltrials.gov] study identifier: NCT01683071; prospectively registered on September 7, 2012). The study was conducted in two parts at 23 U.S. medical centers: dose ranging (part 1) and treatment (part 2). In part 1, the primary objective was to evaluate three liposome bupivacaine doses *versus* placebo and select an optimal dose from among these for part 2. In part 2, the primary objective was to evaluate the selected dose of liposome bupivacaine *versus* placebo with respect to efficacy and safety.

Because this study involved an off-label use of liposome bupivacaine, an Investigational New Drug application (No. 69,198) was approved by the FDA before subject enrollment. Individual enrolling centers obtained approval of an institutional review board/independent ethics committee (appendix) that complied with International Council for Harmonisation Good Clinical Practice guidelines and/or the FDA Title 21 of the Code of Federal Regulations Part 56. Written informed consent was obtained from all subjects before undergoing any study-related procedures.

Subject Selection

Male and female subjects aged 18 yr or older scheduled to undergo primary, unilateral TKA under general, spinal, or epidural anesthesia were eligible if classified as American Society of Anesthesiologists physical status classification of 1, 2, or 3; demonstrated adequate motor function by being able to walk unassisted at least 20 m (use of four-legged walker optional); and had no sensory deficit in the distribution of the femoral nerve, as tested by sensitivity to cold. Subjects were excluded if they were pregnant or nursing; were undergoing a concurrent surgical procedure (*e.g.*, bilateral TKA); had a concurrent painful condition that may have required analgesic treatment in the postsurgical period that was not strictly related to study treatment and may have confounded the postsurgical assessments; or had used long-acting opioids, nonsteroidal antiinflammatory drugs, acetaminophen, or aspirin (except low-dose aspirin for cardioprotection) within 3 days before surgery or any opioids within 24 h before surgery. Subjects who had initiated treatment with selective serotonin or norepinephrine reuptake inhibitors, gabapentin, pregabalin, or duloxetine within 1 month before surgery were also excluded.

Study Design

For parts 1 and 2, each subject received a unique randomization code and subject identifier issued by a centralized randomization system. Synteract, Inc. (USA) created the randomization schedule using SAS®, and Premier Research (USA) incorporated the schedule into their interactive Web response system. During part 1, 101 subjects undergoing TKA were randomized in a 1:1:1:1 ratio to receive one of three single-dose administrations (67, 133, or 266 mg) of liposome bupivacaine in a total volume of 20 ml or preservative-free normal saline for injection (placebo) administered in a femoral nerve block under ultrasound guidance. At the conclusion of the block, a femoral nerve catheter was left in place to allow access for administration of perineural local anesthetic as a rescue treatment, if needed. Blood samples for pharmacokinetic analysis were also obtained during part 1. An unblinded dose selection committee reviewed the area under the curve for numeric rating scale score for pain intensity at rest through 72 h (AUC NRS-$R_{0–72}$), total postsurgical opioid consumption, time to first opioid rescue medication, and safety data through 72 h postoperatively. The unblinded dose selection committee then selected the optimal dose for part 2.

During part 2, 196 subjects (none of whom participated in part 1) were randomized in a 1:1 ratio to receive the selected dose of liposome bupivacaine or placebo in a total volume of 20 ml in a single-injection femoral nerve block under ultrasound guidance. At the conclusion of the block, a femoral nerve catheter was left in place to allow access for administration of perineural local anesthetic as a rescue treatment, if needed.

Administration of Study Drug and Rescue Medications

Preoperatively, a single-injection femoral nerve block and perineural catheter were administered under ultrasound guidance, as previously described.[19] All surgeries were

conducted under general, spinal, or epidural anesthesia. Bupivacaine was not used as the spinal anesthetic. The choice of other spinal anesthetic agent or agents was left to the discretion of the attending anesthesiologist. Use of short-acting and ultra–short-acting IV opioids (*e.g.*, fentanyl) was permitted during surgery. However, intraoperative administration of other opioids (including intrathecal opioids) or any other analgesics, local anesthetics (except for spinal anesthesia), or antiinflammatory agents was not permitted except for emergency use to treat an adverse event (AE).

In parts 1 and 2, postsurgical rescue analgesic medications were administered only upon subject request according to a protocol-defined sequence. No other analgesics (including nonsteroidal antiinflammatory drugs) were permitted during the 72-h postsurgical observation period. If a first rescue medication was required, the subject was given a single IV bolus of hydromorphone 0.5 mg. If a second rescue medication was required, the subject was provided with on-demand IV morphine or hydromorphone, administered by a patient-controlled analgesia pump for the remainder of the 72-h study period or until a third rescue medication was requested; if the subject was able to tolerate oral medications, immediate-release oxycodone tablets (no more than 10 mg every 4 h) were available. If a third rescue medication was required, the subject received a continuous femoral nerve block of bupivacaine HCl 0.125% (1.25 mg/ml), administered *via* the previously inserted femoral nerve catheter at a rate of 8 ml/h for up to 12 h. Any subject who failed to achieve adequate analgesia after three rescue treatments was withdrawn from the study and followed only for safety. For subjects who were withdrawn, analgesia was provided in accordance with standard practice at the individual study site.

Postsurgical Assessments

During part 1 only, blood samples for pharmacokinetic assessments were drawn at baseline, 15 min, 30 min, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 h after starting administration of study medication.

Pain intensity assessments were conducted at baseline (before nerve block administration), at 2, 4, 8, 12, 24, 36, 48, 60, and 72 h postsurgery, and at the first request for rescue analgesia. Pain was assessed using an 11-point NRS (0 = no pain; 10 = worst possible pain) at rest and upon activity, the latter defined as active flexion of involved knee 45 degrees or less. Sensitivity to cold was assessed at baseline and at 2, 4, 12, 24, 36, 48, 60, and 72 h after surgery or until sensitivity to cold had returned in two consecutive evaluations. Motor function was assessed during the acute postsurgical period and on day 30 by measuring the subject's ability to walk 20 m on a level surface with or without use of a four-legged walker. Long-term rehabilitation outcomes were not assessed.

Subjects also completed an overall benefit of analgesic score (OBAS) questionnaire at 24, 48, and 72 h. The OBAS questionnaire is a validated, multidimensional tool that assesses pain intensity, opioid-related AEs, and overall subject satisfaction with pain treatment (table 1).[20] Subject satisfaction with pain control and physician satisfaction with return of sensory/motor function were assessed using a 5-point Likert scale (from "extremely dissatisfied" to "extremely satisfied") at 72 h and on day 30. During part 1 only, subjects were also assessed for predefined treatment-emergent opioid-related AEs.

Outcome Measures

Efficacy outcomes were assessed for all subjects who received study drug and underwent the surgery as planned and consisted of the primary outcome (AUC NRS-$R_{0–72}$), secondary outcomes (total opioid consumption through 72 h and time to first use of opioid rescue medication), and tertiary outcomes (NRS-R and NRS with activity [NRS-A] scores at each assessed time point; AUC of NRS-R scores from 0 to 24, 24 to 48, and 48 to 72 h; total opioid consumption from 0 to 24, 24 to 48, and 48 to 72 h; AUC of NRS-A scores from 0 to 24 and 0 to 72 h; proportion of subjects who were pain-free [NRS-R score of 0 or 1] at each time point; cumulative total opioid consumption at 24, 36, 48, and 60 h; OBAS questionnaire results at 24, 48, and 72 h; subject satisfaction with postsurgical pain control at 72 h and at day 30; and time to subject's return of sensitivity to cold). Specific opioid doses were converted to IV morphine equivalent doses.

Pharmacokinetic parameters (assessed only during part 1 of the study) were calculated from the plasma bupivacaine concentration–time profiles by noncompartmental analysis and included plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), AUC from time 0 to last collection time after drug administration ($AUC_{0–tlast}$), AUC

Table 1. Overview of the Overall Benefit of Analgesic Score Survey

1. Please rate your current pain at rest on a scale between 0 = minimal pain and 4 = maximum imaginable pain.
2. Please grade any distress and bother from vomiting in the past 24 h (0 = not at all to 4 = very much).
3. Please grade any distress and bother from itching in the past 24 h (0 = not at all to 4 = very much).
4. Please grade any distress and bother from sweating in the past 24 h (0 = not at all to 4 = very much).
5. Please grade any distress and bother from freezing in the past 24 h (0 = not at all to 4 = very much).
6. Please grade any distress and bother from dizziness in the past 24 h (0 = not at all to 4 = very much).
7. How satisfied are you with your pain treatment during the past 24 h (0 = not at all to 4 = very much)?

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from time 0 extrapolated to infinity after drug administration ($AUC_{0-\infty}$), apparent terminal elimination rate constant (λ_z), and apparent terminal elimination half-life ($t_{1/2\ el}$). Blood samples were drawn at baseline, 15 min, 30 min, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 h after starting administration of study medication. Placebo samples were collected to maintain blinding but were not analyzed.

Safety outcomes were assessed separately, and combined, for all subjects who received study drug in parts 1 or 2 and consisted of AEs (through day 30), vital sign assessments (at baseline and 30 min, 1 h, and 2 h postsurgery), neurologic assessments (at baseline and 15 min, 30 min, and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 60, and 72 h postsurgery), cardiac assessment (electrocardiogram recordings from baseline through 72 h postsurgery), motor function assessments (at baseline and 24 and 72 h postsurgery and on day 30), and assessment of physician satisfaction with return of sensory/motor function (at 72 h and day 30 postsurgery). Electrocardiogram data were continuously recorded *via* a 12-lead electrocardiogram device and interpreted by a centralized reference cardiologist. Electrocardiogram changes were examined using data obtained at the time closest to the actual T_{max} (when available), mean T_{max}, and median T_{max} from each dose group.

Statistical Analysis

Sample size for part 1 was based on the statistician's estimate of a reasonable sample size from extrapolation of data compiled across phases 2 and 3 wound infiltration studies of liposome bupivacaine.[15,17] Sample size for part 2 was based on results from a phase 3 study of liposome bupivacaine *versus* placebo in subjects undergoing hemorrhoidectomy, where mean (SD) AUC of NRS-R_{0-72} scores were 141.6 (100.6) and 202.3 (104.1), respectively.[21] An estimated enrollment of approximately 180 subjects (90 per treatment group) was needed to achieve more than 97% power to detect a difference in means of 61 for the primary efficacy analysis (assuming the common SD is 104) using a two-group *t* test with a significance level of 0.05.

Three subsets of the enrolled study population were analyzed. Safety analyses included all subjects who received study drug and were based on actual treatment received. Efficacy analyses included all subjects in the safety analysis set who underwent surgery as planned and were based on randomized treatment, regardless of actual treatment received. Pharmacokinetic analysis (part 1 only) included all subjects in the safety analysis set who received liposome bupivacaine, provided sufficient blood samples to permit calculation of pharmacokinetic parameters, and did not receive perineural bupivacaine HCl as rescue medication.

Statistical analyses were performed using SAS® Version 9.2 (SAS Institute Inc., USA, 2009). To account for the use of rescue medication and missing NRS pain intensity score data, windowed worst observation carried forward (wWOCF) plus last observation carried forward (LOCF) imputation method was used to calculate the primary efficacy measure (AUC NRS-R_{0-72}). The wWOCF plus LOCF imputation procedure was used as follows: wWOCF—for subjects who took rescue medication, NRS scores recorded within a half-life ("window") of the opioid rescue medication given were replaced by their highest ("worst") NRS scores before taking their first rescue medication. For subjects who required bupivacaine HCl infusion, the "window" for highest NRS scores was considered from start of infusion until 24 h afterward; LOCF—in cases where subjects had missing NRS pain intensity scores, the scores were interpolated in one of three ways: (1) By the median score from other subjects at the same time point in the same treatment group if before the first nonmissing score; (2) By LOCF if after the last nonmissing score; and (3) By linear interpolation if between two nonmissing scores. Liposome bupivacaine was compared with placebo in parts 1 and 2 using analysis of covariance, with treatment as the main effect and baseline NRS-R pain intensity score as the covariate.

Continuous variables were summarized using standard statistical measures including mean, median, SD, minimum/maximum, *P* values, and two-sided 95% CIs, along with number of subjects included in each analysis, and were reported by treatment group. Categorical variables were summarized by treatment group using counts and percentages. Between-group differences were reported using least-squares means (for NRS scores) or as geometric least-squares means (for postsurgical opioid amounts used).

For secondary efficacy measures in parts 1 and 2, total postsurgical opioid consumption through 72 h was compared between the liposome bupivacaine and placebo groups using ANOVA with treatment as the main effect. Opioid medications were first converted to IV morphine equivalents for each subject, and natural logarithmic transformation was applied to the total amount before analysis. Between-group differences were reported using geometric least-squares means. Time to first opioid rescue was computed in hours as the date and time of first opioid rescue minus date and time of end of surgery; these data were analyzed using the Kaplan–Meier method.

For part 2, no multiple comparisons of the primary efficacy variable (AUC NRS-R_{0-72}) were made. The two secondary efficacy variables (total opioid consumption through 72 h and time to first opioid use) were only to be analyzed using a hierarchical fixed-sequence stepwise testing procedure if the primary efficacy variable was statistically significant ($P \leq 0.05$). To avoid a type 1 error, the testing was performed in a sequentially rejective fashion. First, total postsurgical opioid consumption through 72 h was tested. If the test of opioid consumption was significant ($P \leq 0.05$), time to first opioid rescue medication was tested. Each test was declared positive at the two-sided 0.05 significance level. The significance level for probability values from between-group comparisons of tertiary efficacy variables were adjusted for multiplicity using the Bonferroni correction method. In order to determine

whether imputed pain scores had a meaningful effect on cumulative pain scores at rest, a *post hoc* analysis was conducted to calculate AUC NRS-$R_{0–72}$ (the primary end point), as well as AUC NRS-$R_{0–24}$, AUC NRS-$R_{24–48}$, and AUC NRS-$R_{48–72}$, using only unimputed pain scores.

Results

Part 1

A total of 94 subjects received 67 mg (n = 22), 133 mg (n = 24), or 266 mg (n = 24) liposome bupivacaine or placebo (n = 24). For the primary efficacy measure, AUC NRS-$R_{0–72}$, least-squares mean (standard error [SE]) values were 533 ([33] $P = 0.949$), 427 ([32] $P = 0.024$), and 436 ([32] $P = 0.039$) in the liposome bupivacaine 67-, 133-, and 266-mg groups, respectively, compared with 531 (32) in the placebo group (table 2). Regarding secondary efficacy measures, distribution of time to first opioid rescue medication was significantly longer in the liposome bupivacaine 266-mg group compared with placebo (table 3). Several other assessments suggested a better response to the 266-mg dose, most notably at earlier time points tested (table 3). Overall, 86 subjects (92%) experienced an AE during part 1 of the study, 20 (91%) in the liposome bupivacaine 67-mg group, 22 (92%) in the 133-mg group, 21 (88%) in the 266-mg group, and 23 (96%) in the placebo group (table 4). Nausea (47%), pyrexia (28%), dizziness (17%), constipation (13%), and anemia (12%) were the most frequently reported AEs. No subject discontinued study participation due to an AE. Despite no difference in the primary outcome measure between the 133-mg and 266-mg doses, the liposome bupivacaine 266-mg dose was chosen for part 2 of the study, based on a suggestion of a better response earlier not accompanied by meaningfully increased risk of AEs.

Pharmacokinetics. Dose-related increases were observed in mean plasma bupivacaine levels, C_{max}, and AUC values (table 5). The relationship between dose and bupivacaine plasma exposure over time suggests that liposome bupivacaine demonstrates linear pharmacokinetics (fig. 1).

Table 2. Summary of Results from the Primary Efficacy Assessments in Part 1 (Efficacy Analysis Set)

Parameter	Liposome Bupivacaine 67 mg (n = 22)	Liposome Bupivacaine 133 mg (n = 24)	Liposome Bupivacaine 266 mg (n = 24)	Placebo (n = 24)
Least-squares mean (SE) AUC of NRS-$R_{0–72}$ score	533 (33)	427 (32)*	436 (32)*	531 (32)
Median (minimum–maximum) AUC of NRS-$R_{0–72}$ score†	577 (104–711)	415 (69–710)	393 (228–711)	568 (229–710)

*$P < 0.05$ *vs.* placebo; †no inferential statistical analyses were performed to test between-group differences for median values.
AUC = area under the curve; NRS-$R_{0–72}$ = numeric rating scale score for pain intensity at rest through 72 h; SE = standard error.

Table 3. Summary of Results from Secondary and Other Efficacy Assessments in Part 1 (Efficacy Analysis Set)

Parameter	Liposome Bupivacaine 67 mg (n = 22)	Liposome Bupivacaine 133 mg (n = 24)	Liposome Bupivacaine 266 mg (n = 24)	Placebo (n = 24)
Secondary efficacy assessments				
Geometric least-squares mean total postsurgical consumption of opioid rescue medication, mg	101	81	95	111
Median (95% CI) time to first opioid rescue medication, h	0.49 (0.30–0.65)	0.37 (0.28–0.70)	1.29 (0.37–2.35)*	0.41 (0.30–0.55)
Tertiary efficacy assessments				
Mean (SD) NRS-R score at first request for rescue pain medication(s)	7.9 (2.8)	6.9 (2.2)	6.4 (2.4)†	8.3 (1.9)†
Mean (SD) NRS-A score at first request for rescue pain medication(s)	8.1 (2.7)‡	7.3 (2.5)§	6.7 (2.4)†	8.8 (1.6)‡
Mean (SD) AUC of NRS-$R_{0–24}$ score	180 (56)	160 (50)	154 (53)	179 (39)
Median (minimum–maximum) AUC of NRS-$R_{0–24}$ score‖	190 (49–231)	160 (33–234)	146 (68–231)	183 (84–230)
Mean (SD) AUC of NRS-$A_{0–24}$ score	194 (40)	174 (46)	171 (47)	196 (34)
Median (minimum–maximum) AUC of NRS-$A_{0–24}$ score‖	203 (89–231)	169 (41–230)	172 (86–231)	208 (127–230)
Mean (SD) AUC of NRS-$A_{0–72}$ score	592 (127)	499 (144)	503 (145)	587 (115)
Median (minimum–maximum) AUC of NRS-$A_{0–72}$ score‖	624 (221–711)	502 (77–710)	480 (297–711)	625 (367–710)

*$P < 0.05$ *vs.* placebo; †n = 22; ‡n = 20; §n = 23; ‖no inferential statistical analyses were performed to test between-group differences for median values.
AUC = area under the curve; NRS-$A_{0–24}$/NRS-$R_{0–24}$ = numeric rating scale score for pain intensity with activity/at rest through 24 h; NRS-$A_{0–72}$ = numeric rating scale score for pain intensity with activity through 72 h.

Table 4. Most Commonly Reported Treatment-Emergent AEs

AE	Part 1 of Study: Liposome Bupivacaine 67 mg (n = 22), n (%)	Liposome Bupivacaine 133 mg (n = 24), n (%)	Liposome Bupivacaine 266 mg (n = 24), n (%)	Placebo (n = 24), n (%)	Part 2 of Study: Liposome Bupivacaine 266 mg (n = 92), n (%)	Placebo (n = 92), n (%)
Subjects with ≥1 AE	20 (91)	22 (92)	21 (88)	23 (96)	88 (96)	88 (96)
Nausea	8 (36)	14 (58)	13 (54)	9 (38)	49 (53)	61 (66)
Pyrexia	8 (36)	7 (29)	8 (33)	3 (13)	28 (30)	24 (26)
Constipation	3 (14)	2 (8)	6 (25)	1 (4)	32 (35)	32 (35)
Pruritus	1 (5)	2 (8)	2 (8)	2 (8)	33 (36)	31 (34)
Vomiting	1 (5)	0	1 (4)	2 (8)	26 (28)	38 (41)
Dizziness	3 (14)	3 (13)	4 (17)	6 (25)	15 (16)	19 (21)
Insomnia	1 (5)	2 (8)	2 (8)	4 (17)	5 (5)	11 (12)
Anemia	4 (18)	1 (4)	4 (17)	2 (8)	8 (9)	5 (5)
Hyperhidrosis	0	0	1 (4)	1 (4)	10 (11)	11 (12)
Procedural hypotension	2 (9)	2 (8)	3 (13)	0	10 (11)	6 (7)
Urinary retention	1 (5)	0	0	0	12 (13)	6 (7)
Headache	1 (5)	3 (13)	2 (8)	1 (4)	5 (5)	4 (4)
Pruritus generalized	0	1 (4)	0	3 (13)	2 (2)	2 (2)

Adverse events (AEs) among subjects who received liposome bupivacaine or placebo during study parts 1 and 2, including all AEs reported by ≥ 10% of subjects in any treatment group (safety analysis set).

Table 5. Pharmacokinetic Parameters for Liposome Bupivacaine 67, 133, and 266 mg in Study Part 1

Parameter	Liposome Bupivacaine Dose: 67 mg, n = 19	133 mg, n = 19	266 mg, n = 21
C_{max}, ng/ml	146 (91)	282 (127)	577 (289)
T_{max}, h	65.9 (4.0–73.6)	72.0 (0.6–74.3)	72.0 (24.9–94.3)
$AUC_{0–72}$, h•ng/ml	5,589 (3,198)	10,513 (4,817)	18,311 (8,690)
$AUC_{0–\infty}$, h•ng/ml	8,252 (2,103)	18,452 (12,092)	34,491 (5,297)
λ_z, 1/h	0.0413 (0.0207)	0.0426 (0.0283)	0.0437 (0.0202)
$t_{1/2}$, h	20.5 (10.5)	29.0 (24.4)	18.2 (6.5)

Summary of pharmacokinetic parameters for liposome bupivacaine doses (67, 133, and 266 mg) evaluated in study part 1. Data are reported as mean (SD), except for T_{max}, which is reported as median (minimum–maximum) (pharmacokinetic analysis set).

λ_z = apparent terminal elimination rate constant; $AUC_{0–72}$ = area under the plasma concentration *vs.* time curve from time 0 to 72 h after drug administration; $AUC_{0–\infty}$ = AUC from time 0 extrapolated to infinity after drug administration; C_{max} = peak plasma concentration; $t_{1/2}$ = apparent terminal elimination half-life; T_{max} = time to peak plasma concentration.

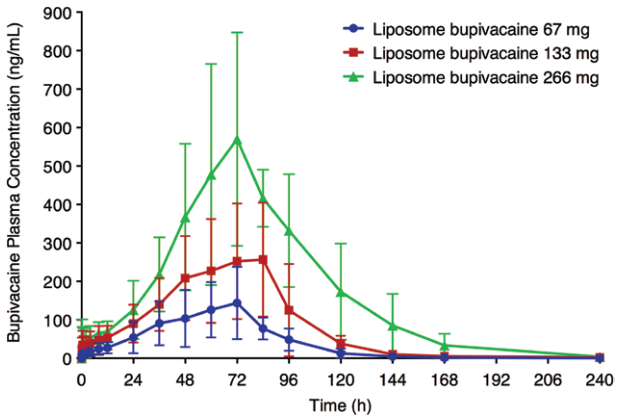

Fig. 1. Plasma concentration *versus* time curves after single administration of liposome bupivacaine 67 mg (*blue*), 133 mg (*red*), and 266 mg (*green*) in a femoral nerve block during study part 1. Data shown as mean values ± SD (*error bars*).

Part 2

A total of 184 subjects received liposome bupivacaine or placebo (liposome bupivacaine, n = 92; placebo, n = 92) and 164 completed the study (table 6 and fig. 2). In the liposome bupivacaine group, 26% of NRS-R pain intensity scores were not imputed, 69% were imputed due to use of rescue medication, and 5% were interpolated due to a missing value. In the placebo group, 24% of NRS-R scores were not imputed, 70% were imputed due to use of rescue medication, and 6% were interpolated due to a missing value.

Primary Outcome Measure. Least-squares mean (SE) AUC NRS-$R_{0–72}$ was lower in the liposome bupivacaine group than in the placebo group (419 [17] *vs.* 516 [17], respectively; $P < 0.0001$; table 7). In the analysis without imputation, least-squares mean AUC NRS-$R_{0–72}$ remained significantly lower with liposome bupivacaine *versus* placebo (221 [12] *vs.* 282 [12]; $P = 0.0005$).

Table 6. Subject Demographics and Baseline Attributes in Study Part 2

Attribute	Liposome Bupivacaine (n = 92)	Placebo (n = 92)*	All Subjects (N = 184)
Age, yr, mean (SD)	66 (10)	64 (9)	65 (10)
Gender, n (%)			
Male	40 (44)	35 (38)	75 (41)
Female	52 (57)	57 (62)	109 (59)
Race/ethnicity, n (%)			
White	75 (82)	77 (84)	152 (83)
Black/African American	15 (16)	14 (15)	29 (16)
American Indian†	0	2 (2)	2 (1)
Asian	2 (2)	0	2 (1)
ASA physical status, n (%)			
1	7 (8)	3 (3)	10 (5)
2	38 (41)	49 (53)	87 (47)
3	47 (51)	40 (44)	87 (47)
Height, cm, mean (SD)	170 (11)	169 (11)	170 (11)
Weight, kg, mean (SD)	93 (21)	91 (18)	92 (19)
Type of surgical anesthesia administered, n (%)			
General	62 (67)	56 (62)	118 (65)
Spinal	28 (30)	35 (39)	63 (35)
Other‡	2 (2)	0	2 (1)

Summary of subject demographics and baseline attributes from part 2 of study (safety analysis set).

*Placebo n = 91 for height, weight, and surgical anesthesia data. †Includes Alaskan Natives. ‡One subject received a combination of spinal and epidural anesthesia plus sedation; one subject received spinal anesthesia, which was ineffective, followed by general anesthesia.

ASA = American Society of Anesthesiologists.

Secondary Outcome Measures. Subjects in the liposome bupivacaine group used less total postsurgical opioids through 72 h than those in the placebo group (geometric least-squares mean IV morphine equivalents 76 *vs.* 103 mg, respectively; P = 0.0016); between-group differences in cumulative opioid consumption were maintained through 24 h (46 *vs.* 60 mg, respectively), 36 h (58 *vs.* 77 mg, respectively), 48 h (66 *vs.* 89 mg, respectively), and 60 h (72 *vs.* 98 mg, respectively; $P \leq 0.0058$ for each comparison). Median time to first use of opioid rescue medication was similar between the liposome bupivacaine and placebo groups (0.44 *vs.* 0.43 h; P = 0.9556).

Tertiary Outcome Measures. Between-group differences in mean (SD) NRS-R at first request for rescue pain medication, AUC of NRS-$R_{0–24}$, AUC of NRS-$A_{0–24}$, and AUC of NRS-$A_{0–72}$ scores, and geometric least-squares mean amount of postsurgical opioid rescue medications consumed from 0 to 24 h were lower in the liposome bupivacaine group *versus* placebo (table 8). Least-squares mean (SE) AUCs of NRS-R scores were significantly lower ($P < 0.0083$) in the liposome bupivacaine group during each 24-h interval (0 to 24, 24 to 48, and 48 to 72 h) after surgery (fig. 3). Between-group differences in the least squares mean (SE) in favor of liposome bupivacaine *versus* placebo were −29.0 (7.6) (P = 0.0002) during the first 24 h postsurgery, −29.1 (8.6) (P = 0.0009) during 24 to 48 h postsurgery, and −38.4 (10.2) (P = 0.0002) during 48 to 72 h postsurgery. In the analysis without imputation, least-squares mean (SE) cumulative pain scores at rest remained significantly lower in the liposome bupivacaine group *versus* placebo during the first day (AUC NRS-$R_{0–24}$, 68 [3] *vs.* 80 [3], respectively; P = 0.0051) and second day after surgery (AUC NRS-$R_{24–48}$, 82 [5] *vs.* 112 [5], respectively; $P < 0.0001$), but not on day 3 (AUC NRS-$R_{48–72}$, 66 [7] *vs.* 83 [7], respectively; P = 0.0736).

Least-squares mean (SE) NRS-R and NRS-A scores through 72 h are shown in figures 4 and 5, respectively. Least-squares mean NRS-R scores were lower in the liposome bupivacaine group than in the placebo group at 2, 4, 12, and 24 h postsurgery (fig. 4). The between-group difference in least-squares mean NRS-R scores ranged from as high as 1.6 at 2 h after surgery to as low as 0.5 at 60 h after surgery. Least-squares mean NRS-A scores were lower in the liposome bupivacaine group than in placebo groups at 24 and

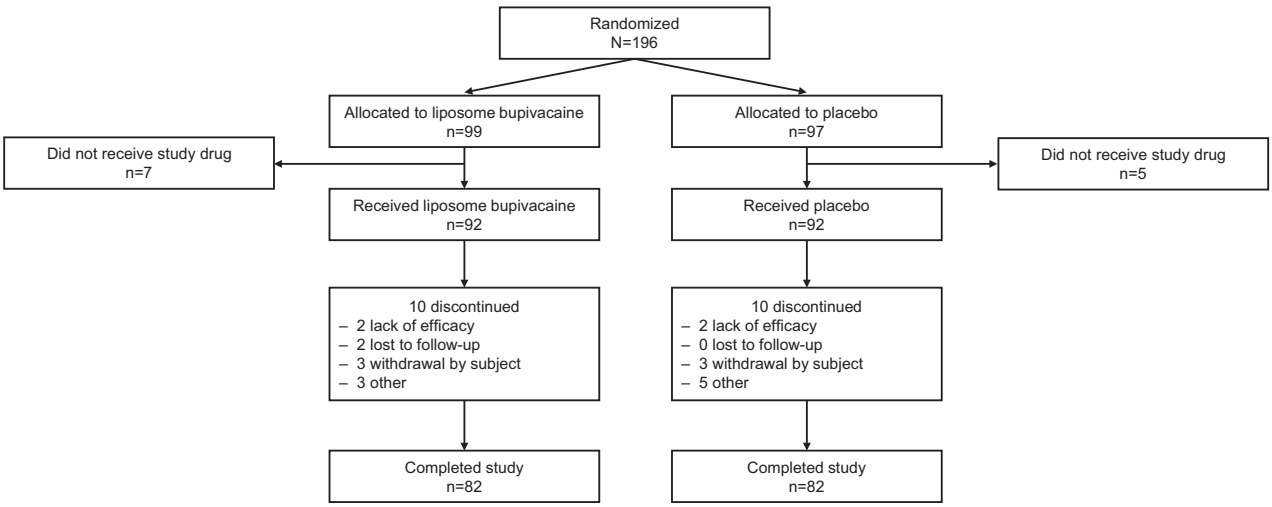

Fig. 2. Subject disposition in study part 2.

Table 7. Summary of Results from the Primary Efficacy Assessments in Part 2 (Efficacy Analysis Set)

Parameter	Liposome Bupivacaine 266 mg (n = 92)	Placebo (n = 91)
Least-squares mean (SE) AUC of NRS-$R_{0–72}$ score	419 (17)*	516 (17)
Median (minimum–maximum) AUC of NRS-$R_{0–72}$ score†	398 (68–710)	518 (175–710)

*P < 0.0001 *vs.* placebo; †no inferential statistical analyses were performed to test between-group differences for median values.
AUC = area under the curve; NRS-$R_{0–72}$ = numeric rating scale score for pain intensity at rest through 72 h; SE = standard error.

Table 8. Summary of Results from Secondary and Tertiary Assessments in Part 2 (Efficacy Analysis Set)

Parameter	Liposome Bupivacaine 266 mg (n = 92)	Placebo (n = 91)
Secondary efficacy assessments		
Geometric least-squares mean total postsurgical consumption of opioid rescue medication, mg	76*	103
Median (95% CI) time to first opioid rescue medication, h	0.44 (0.40–0.53)	0.43 (0.37–0.57)
Tertiary efficacy assessments		
Mean (SD) NRS-R score at first request for rescue pain medication(s)	6.8 (2.5)†	7.8 (2.3)‡
Mean (SD) NRS-A score at first request for rescue pain medication(s)	7.5 (2.3)§	8.2 (2.2)‖
Mean (SD) AUC of NRS-$R_{0–24}$ score	152 (55)#	180 (49)
Median (minimum–maximum) AUC of NRS-$R_{0–24}$ score**	151 (28–230)	201 (68–231)
Mean (SD) AUC of NRS-$A_{0–24}$ score	172 (48)††	191 (43)
Median (minimum–maximum) AUC of NRS-$A_{0–24}$ score**	184 (63–230)	207 (82–231)
Mean (SD) AUC of NRS-$A_{0–72}$ score	497 (146)‡‡	565 (135)
Median (minimum–maximum) AUC of NRS-$A_{0–72}$ score**	524 (188–710)	592 (178–710)
Geometric least-squares mean postsurgical consumption of opioid rescue medication from 0 to 24 h, mg	46§§	60
Geometric least-squares mean postsurgical consumption of opioid rescue medication from 24 to 48 h, mg	16	23
Geometric least-squares mean postsurgical consumption of opioid rescue medication from 48 to 72 h, mg	7	11

*P < 0.01 *vs.* placebo; †n = 89, P = 0.0028 *vs.* placebo; ‡n = 86; §n = 81; ‖n = 76; #P = 0.0002 *vs.* placebo; **no inferential statistical analyses were performed to test between-group differences for median values; ††P = 0.0053 *vs.* placebo; ‡‡P = 0.0006 *vs.* placebo; §§P = 0.0058 *vs.* placebo.
AUC = area under the curve; NRS-$A_{0–24}$/NRS-$R_{0–24}$ = numeric rating scale score for pain intensity with activity/at rest through 24 h; NRS-$A_{0–72}$ = numeric rating scale score for pain intensity with activity through 72 h.

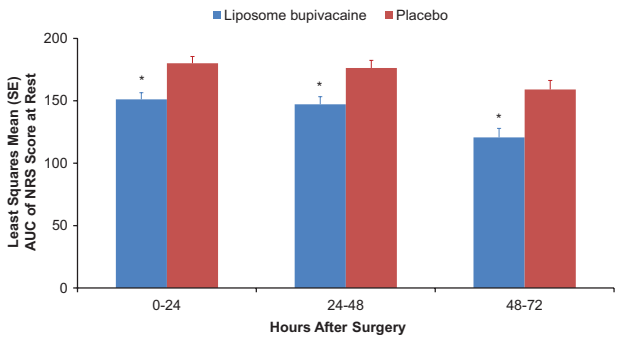

Fig. 3. Least-squares mean (standard error [SE]) area under the curve (AUC) of numeric rating scale (NRS) pain scores at rest during three successive 24-h periods (0 to 24, 24 to 48, and 48 to 72 h) after total knee arthroplasty for subjects receiving liposome bupivacaine 266 mg (*blue bars*) or placebo (*red bars*) in study part 2. All between-group differences were statistically significant (*P < 0.0083).

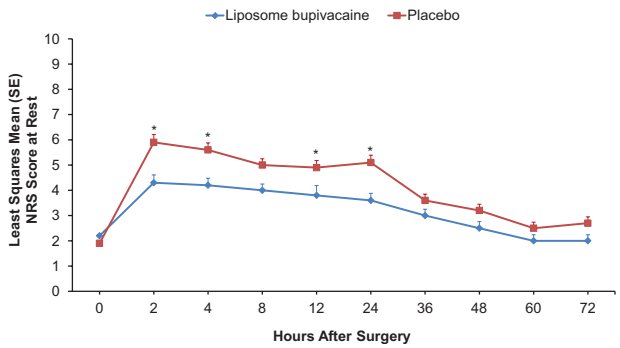

Fig. 4. Least-squares mean (standard error [SE]) numeric rating scale (NRS) pain scores at rest among total knee arthroplasty subjects receiving liposome bupivacaine 266 mg (*blue line*) or placebo (*red line*) through 72-h postsurgery in study part 2. *Asterisks* indicate statistically significant (P < 0.005) between-group differences.

60 h after surgery (fig. 5). The between-group difference in least-squares mean NRS-A scores ranged from as high as 1.3 at 2 and 24 h after surgery to as low as 0.5 at 36 h after surgery. The mean NRS-A pain intensity scores remained in the moderate range in both the liposome bupivacaine and placebo groups throughout the part 2 study period.

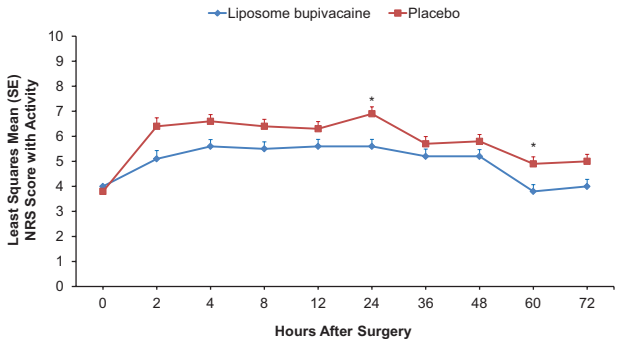

Fig. 5. Least-squares mean (standard error [SE]) numeric rating scale (NRS) pain scores with activity among total knee arthroplasty subjects receiving liposome bupivacaine 266 mg (*blue line*) or placebo (*red line*) through 72-h post-surgery in study part 2. *Asterisks* indicate statistically significant ($P < 0.0055$) between-group differences.

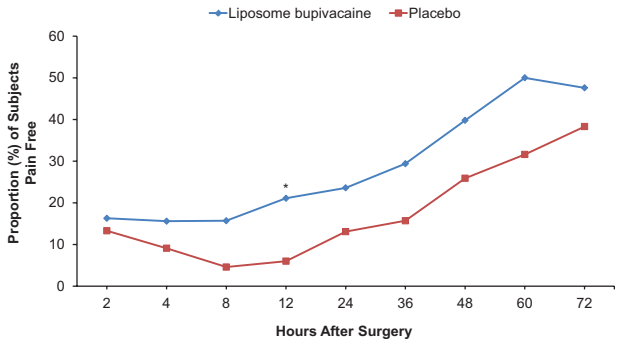

Fig. 6. Proportion of subjects receiving liposome bupivacaine 266 mg (*blue line*) or placebo (*red line*) who reported being pain-free (numeric rating scale score of 0 or 1) through 72 h after total knee arthroplasty in study part 2. *Asterisk* indicates statistically significant ($P < 0.005$) between-group differences.

All subjects required at least some rescue medication (table 9), with no difference between groups (P = not significant [NS]). Pain was sufficiently severe to require the first and then a second opioid rescue medication in 92% of subjects in the liposome bupivacaine group compared with 81% in the placebo group.

More subjects treated with liposome bupivacaine were pain-free at 12 h postsurgery (fig. 6; $P = 0.0038$). The proportion of subjects treated with liposome bupivacaine who were pain-free increased steadily after 8 through 60 h postsurgery, while the proportion of subjects treated with placebo who were pain-free decreased between 2 and 8 h before increasing at 12 h after surgery.

With respect to subject-reported outcomes, mean OBAS was lower (indicating superior analgesia) among subjects receiving liposome bupivacaine compared with placebo at 24 (5.6 *vs.* 7.3, respectively; $P = 0.0011$) and 72 h (3.1 *vs.* 4.1; $P = 0.0072$) postsurgery. In contrast, there was no difference in the proportion of subjects who were "satisfied" or "extremely satisfied" with their pain control at 72 h (92 *vs.* 84%; P = NS) and at day 30 (89 *vs.* 83%; P = NS). Median time to sensitivity to cold was 1.85 h (95% CI, 0.48 to 2.02) in the liposome bupivacaine group compared with 1.88 h (95% CI, 0.45 to 2.00) in the placebo group (P = NS).

Table 9. Subjects Who Received Rescue Medication in Study Part 2

Parameter	Liposome Bupivacaine 266 mg (n = 92) n (%)	Placebo (n = 91) n (%)
Received no rescue medication	0	0
Received only the first rescue medication	0	0
Received the first and a second rescue medication	85 (92)	74 (81)
Received all three rescue medications	7 (8)	17 (19)

Proportion of subjects who received rescue medication through 72 h in part 2 of the study (efficacy analysis set).

Safety

In part 2, 176 subjects (96%) experienced at least one AE, 88 (96%) in each treatment group. Frequency of specific AEs was generally similar between treatment groups (table 4). Nausea (60%), constipation (35%), pruritus (35%), vomiting (35%), and pyrexia (28%) were the most frequently reported AEs. At least one serious AE was reported by eight subjects (9%) receiving liposome bupivacaine 266 mg and nine subjects (10%) receiving placebo. Each of the serious AEs was judged by the study investigator to be unrelated to study drug. There were no discontinuations due to an AE, and there were no deaths during the study.

In parts 1 and 2 combined, physician satisfaction with return of sensory/motor function was rated as "satisfied" or "extremely satisfied" for 89% of subjects receiving liposome bupivacaine 266 mg at 72 h postsurgery *versus* 95% of subjects who received placebo. On day 30, proportions of "satisfied" or "extremely satisfied" ratings were 96 and 97%, respectively. Overall, the proportion of subjects completing the 20-m walk test was similar between treatment groups at 24 h after surgery (51% [55 of 107], liposome bupivacaine 266 mg *vs.* 56% [58 of 103], placebo), at 72 h after surgery (83% [86 of 104] *vs.* 89% [90 of 101]), and on day 30 (99% [103 of 104] *vs.* 100% [100 of 100]). No falls occurred during part 1 of the study. Three falls were reported during part 2, and each occurred in the liposome bupivacaine group (3.3% of subjects treated with liposome bupivacaine). One 63-yr-old female subject fell after getting up from the toilet. The second fall occurred when an 81-yr-old male subject attempted to walk to the bathroom without assistance. The third fall occurred when a 66-yr-old male subject was attempting to sit on the toilet but missed the seat. None of the subjects sustained injuries or complications due to their fall; investigators judged that the study drug was related to the fall only in one subject. All subjects who experienced

a fall were nonetheless able to complete a 20-m walk test at 24 h, 72 h, and 30 days after surgery and reported that they were "satisfied" and/or "extremely satisfied" with their pain control at 72 h and on day 30. The treating physicians for these three subjects reported that they were satisfied with return of motor function at all timed assessments.

Incidence of "solicited neurologic events" (including oral/perioral numbness, metallic taste, hearing problems, vision problems, or muscle twitching) was low in both groups at all tested time points through 72 h. The highest incidence occurred at the 12-h time point in the placebo group (7% [7]; 2% [2] in the liposome bupivacaine 266-mg group). Investigators checked plasma bupivacaine levels at the time of a solicited event if they felt it clinically relevant; maximum plasma concentration for any of these subjects was 829 ng/ml.

Electrocardiogram data demonstrated no clinically relevant signal, suggesting drug-related changes in heart rate, atrioventricular conduction (measured by PR interval duration), cardiac depolarization (measured by QRS interval duration), cardiac wave form morphology, or new arrhythmias.

Discussion

This two-part study was designed to evaluate efficacy and safety of liposome bupivacaine when administered in a femoral nerve block for analgesia in subjects having unilateral TKA. Based on results from part 1 (dose ranging), the unblinded dose selection committee recommended 266 mg of liposome bupivacaine for part 2 of the study. Dose selection was based on the observation that some secondary and tertiary assessments of the 266-mg dose suggested better analgesia compared with the 133-mg dose although these doses did not differ in the primary outcome measure.

Results from the primary and secondary efficacy analyses showed that liposome bupivacaine 266 mg in a femoral nerve block was associated with a modest but statistically significant reduction in cumulative pain intensity scores and opioid consumption through 72 h postsurgery compared with placebo. Results from the per-protocol tertiary analyses, which included imputed pain scores, showed that AUC of NRS scores for pain at rest were lower in the liposome bupivacaine group during all three of the 24-h intervals (0 to 24, 24 to 48, and 48 to 72 h) after surgery. However, a *post hoc* analysis of cumulative pain scores, which included only unimputed pain scores, showed a significant difference in favor of liposome bupivacaine only during the 0- to 24-h and 24- to 48-h periods after surgery. In the *post hoc* analysis, the between-group difference did not reach statistical significance during the 48- to 72-h interval after surgery. It should also be noted that pain was sufficiently severe to require second-step rescue with opioids *via* intravenously administered patient-controlled analgesia in the vast majority of subjects in both treatment groups, and mean subject-reported pain intensity scores with activity remained in the "moderate" range in both treatment groups during part 2 of the study, even with the use of opioid rescue analgesia in the majority of study subjects.

The proportion of subjects who were pain-free was greater in the liposome bupivacaine group compared with placebo beginning at 2 h after surgery. Interestingly, median time to first use of opioid rescue medication was nearly identical (≈0.4 h) in the treatment groups, in contrast to the longer time (1.29 h) with liposome bupivacaine in the liposome bupivacaine 266-mg group (n = 24) in part 1. This finding may be explained by occurrence of the pain in the sciatic nerve distribution, which could have been unaffected by the study intervention.

The rate of AEs in the liposome bupivacaine group was similar to that in the placebo group. There was no apparent impact on motor function; nor were there any clinically meaningful changes in neurologic or cardiac function. While the study was not powered to detect between-group differences in incidence of patient falls, the observed fall rate in the current study (3.3%) was consistent with rates of 1 to 2% reported recently in a retrospective study of more than 191,000 patients who underwent TKA under general, neuraxial, or combined anesthesia.[22] That study also showed no relationship between use of peripheral nerve block and risk for falls. Subjects in the liposome bupivacaine group consumed a significantly lower mean amount of opioids after surgery than those in the placebo group; the incidences of AEs commonly associated with opioid use (*e.g.*, nausea, constipation, pruritus, vomiting) were similar in the two treatment groups, and this lack of effect of modest reduction in opioid use on opioid-induced side effects has been observed with other adjunctive analgesic treatments.[10,23–27]

Because the knee joint is innervated by both the sciatic and femoral nerves, a combination of femoral and sciatic nerve block may provide superior pain relief and reduced opioid consumption in patients undergoing TKA compared with femoral nerve block alone.[2] Thus, a limitation of the current study is that the sciatic block was not used in any subjects enrolled, potentially underestimating the analgesic benefit of long-duration femoral block with liposome bupivacaine. In addition, we could not account for potential effects associated with interactions between liposome bupivacaine and bupivacaine HCl (aqueous bupivacaine) administered into the same tissue space *via* femoral nerve catheter for rescue analgesia. It should also be emphasized that the study evaluated liposome bupivacaine for postsurgical analgesia only; we did not evaluate its use for intraoperative anesthesia in this study. Also, long-term rehabilitative outcomes were not assessed, and detailed quantitative data on the potential effects of liposome bupivacaine on quadriceps weakness were not collected.

In this multicenter, randomized, placebo-controlled study, a single-injection femoral nerve block using liposome bupivacaine provided postoperative analgesia and reduced opioid requirements for 48 h or more in subjects undergoing TKA. Use of a long-acting, single-injection nerve block compared to a continuous infusion can eliminate some catheter-related risks such as dislodgement, infection, and undesired retention. Not having to carry a reservoir of local

anesthetic during an infusion could also lead to secondary benefits such as increased ability to conduct rehabilitation therapy and earlier ambulation.[11,28] While the results of this study showed that a single administration of liposome bupivacaine can provide analgesia that lasts at least 2 days when used in femoral nerve block, more information is clearly needed in order to better define the potential role of liposome bupivacaine in this surgical setting. Future prospective studies are required to assess the relative safety and efficacy of liposome bupivacaine compared with current standard-of-care postoperative analgesic regimens. At the writing of this article, liposome bupivacaine is not approved for use in peripheral nerve blocks. Based, in part, on the results of this study, a supplemental new drug application for liposome bupivacaine in support of a nerve block indication has been submitted to the U.S. FDA.

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Competing Interests

Dr. Hadzic has consulted and advised for SkyePharma, London, United Kingdom; GE, Fairfield, Connecticut; SonoSite, Bothell, Washington; Codman & Shurtleff, Inc., a division of Johnson & Johnson Health Care Systems, Inc., Raynham, Massachusetts; Cadence Pharmaceuticals, Inc., San Diego, California; Pacira Pharmaceuticals, Inc., Parsippany, New Jersey; Baxter, Deerfield, Illinois; and B. Braun Medical, Inc., Bethlehem, Pennsylvania. He has also received research funding from Glaxo Smith-Kline, Brentford, United Kingdom; Pacira Pharmaceuticals, Inc.; and Baxter. Dr. Hadzic receives royalty income from B. Braun Medical, Inc. Dr. Minkowitz has been a consultant for Pacira Pharmaceuticals, Inc., Parsippany, New Jersey. He has also received research funding from Pacira Pharmaceuticals, Inc.; Innocoll Pharmaceuticals, Newtown Square, Pennsylvania; and DURECT Corporation, Cupertino, California. Dr. Melson has received research grants from Pacira Pharmaceuticals, Inc. Dr. Berkowitz is a stockholder of Pacira Pharmaceuticals, Inc. Ms. Lookabaugh is a consultant for Pacira Pharmaceuticals, Inc. Dr. Ilfeld's institution has received funding for his research from SPR Therapeutics, Cleveland, Ohio; Baxter Healthcare, Deerfield, Illinois; Smiths Medical, St. Paul, Minnesota; Summit Medical, Inc., Sandy, Utah; Teleflex Medical, Research Triangle Park, Durham, North Carolina; Myoscience, Fremont, California; and Pacira Pharmaceuticals, Inc. In addition, Dr. Ilfeld has been a consultant for Pacira Pharmaceuticals, Inc. The other authors declare no competing interests.

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Full protocol available from Ms. Lookabaugh: janice.lookabaugh@pacira.com. Raw data available from Ms. Lookabaugh: janice.lookabaugh@pacira.com.

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References

1. Allen HW, Liu SS, Ware PD, Nairn CS, Owens BD: Peripheral nerve blocks improve analgesia after total knee replacement surgery. Anesth Analg 1998; 87:93–7
2. Cook P, Stevens J, Gaudron C: Comparing the effects of femoral nerve block *versus* femoral and sciatic nerve block on pain and opiate consumption after total knee arthroplasty. J Arthroplasty 2003; 18:583–6
3. Bonica JJ: Postoperative pain, The Management of Pain. Edited by Bonica JJ. Malvern, PA, Lea & Febiger, 1990, pp 461–80
4. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F: Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology 1999; 91:8–15
5. Singelyn FJ, Deyaert M, Joris D, Pendeville E, Gouverneur JM: Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. Anesth Analg 1998; 87:88–92
6. Paul JE, Arya A, Hurlburt L, Cheng J, Thabane L, Tidy A, Murthy Y: Femoral nerve block improves analgesia outcomes after total knee arthroplasty: A meta-analysis of randomized controlled trials. Anesthesiology 2010; 113:1144–62
7. Szczukowski MJ Jr, Hines JA, Snell JA, Sisca TS: Femoral nerve block for total knee arthroplasty patients: A method to control postoperative pain. J Arthroplasty 2004; 19:720–5
8. Duarte VM, Fallis WM, Slonowsky D, Kwarteng K, Yeung CK: Effectiveness of femoral nerve blockade for pain control after total knee arthroplasty. J Perianesth Nurs 2006; 21:311–6
9. Good RP, Snedden MH, Schieber FC, Polachek A: Effects of a preoperative femoral nerve block on pain management and rehabilitation after total knee arthroplasty. Am J Orthop (Belle Mead NJ) 2007; 36:554–7
10. Seet E, Leong WL, Yeo AS, Fook-Chong S: Effectiveness of 3-in-1 continuous femoral block of differing concentrations compared to patient controlled intravenous morphine for post total knee arthroplasty analgesia and knee rehabilitation. Anaesth Intensive Care 2006; 34:25–30
11. Ilfeld BM: Continuous peripheral nerve blocks: A review of the published evidence. Anesth Analg 2011; 113: 904–25
12. Ilfeld BM, Enneking FK: Continuous peripheral nerve blocks at home: A review. Anesth Analg 2005; 100:1822–33
13. Cuvillon P, Ripart J, Lalourcey L, Veyrat E, L'Hermite J, Boisson C, Thouabtia E, Eledjam JJ: The continuous femoral nerve block catheter for postoperative analgesia: Bacterial colonization, infectious rate and adverse effects. Anesth Analg 2001; 93:1045–9
14. Exparel [prescribing information]. Parsippany, Pacira Pharmaceuticals, Inc., 2015
15. Bergese SD, Ramamoorthy S, Patou G, Bramlett K, Gorfine SR, Candiotti KA: Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. J Pain Res 2012; 5:107–16

16. Dasta J, Ramamoorthy S, Patou G, Sinatra R: Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. Curr Med Res Opin 2012; 28:1609–15
17. Viscusi ER, Sinatra R, Onel E, Ramamoorthy SL: The safety of liposome bupivacaine, a novel local analgesic formulation. Clin J Pain 2014; 30:102–10
18. Ilfeld BM, Malhotra N, Furnish TJ, Donohue MC, Madison SJ: Liposomal bupivacaine as a single-injection peripheral nerve block: A dose-response study. Anesth Analg 2013; 117:1248–56
19. Mariano ER, Loland VJ, Sandhu NS, Bellars RH, Bishop ML, Afra R, Ball ST, Meyer RS, Maldonado RC, Ilfeld BM: Ultrasound guidance *versus* electrical stimulation for femoral perineural catheter insertion. J Ultrasound Med 2009; 28:1453–60
20. Lehmann N, Joshi GP, Dirkmann D, Weiss M, Gulur P, Peters J, Eikermann M: Development and longitudinal validation of the overall benefit of analgesia score: A simple multi-dimensional quality assessment instrument. Br J Anaesth 2010; 105:511–8
21. Gorfine SR, Onel E, Patou G, Krivokapic ZV: Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: A multicenter, randomized, double-blind, placebo-controlled trial. Dis Colon Rectum 2011; 54:1552–9
22. Memtsoudis SG, Danninger T, Rasul R, Poeran J, Gerner P, Stundner O, Mariano ER, Mazumdar M: Inpatient falls after total knee arthroplasty: The role of anesthesia type and peripheral nerve blocks. ANESTHESIOLOGY 2014; 120:551–63
23. Sarridou DG, Chalmouki G, Braoudaki M, Koutsoupaki A, Mela A, Vadalouka A: Intravenous parecoxib and continuous femoral block for postoperative analgesia after total knee arthroplasty. A randomized, double-blind, prospective trial. Pain Physician 2015; 18:267–76
24. Andersen KV, Nikolajsen L, Haraldsted V, Odgaard A, Søballe K: Local infiltration analgesia for total knee arthroplasty: Should ketorolac be added? Br J Anaesth 2013; 111:242–8
25. Jenstrup MT, Jæger P, Lund J, Fomsgaard JS, Bache S, Mathiesen O, Larsen TK, Dahl JB: Effects of adductor-canal-blockade on pain and ambulation after total knee arthroplasty: A randomized study. Acta Anaesthesiol Scand 2012; 56:357–64
26. Casati A, Ostroff R, Casimiro C, Faluhelyi A, Medina J, Fanelli G; Chiropolis Study Group: 72-hour epidural infusion of 0.125% levobupivacaine following total knee replacement: A prospective, randomized, controlled, multicenter evaluation. Acta Biomed 2008; 79:28–35
27. Förster JG, Rosenberg PH: Small dose of clonidine mixed with low-dose ropivacaine and fentanyl for epidural analgesia after total knee arthroplasty. Br J Anaesth 2004; 93:670–7
28. Marhofer D, Marhofer P, Triffterer L, Leonhardt M, Weber M, Zeitlinger M: Dislocation rates of perineural catheters: A volunteer study. Br J Anaesth 2013; 111:800–6

Appendix. List of IRBs/IECs

IRB/IEC Name/Address	Site Number/Principal Investigator
Western Institutional Review Board, 3535 7th Avenue SW, Olympia, WA 98502, USA, T: 360-252-2500, F: 360-252-2498, www.wirb.com	Site 001 Timothy Melson, M.D. Site 003 Juan Carlos Restrepo, M.D. Site 005 Harold Minkowitz, M.D. Site 007 Richard Berkowitz, M.D. Site 009 Mark Hollmann, M.D. Site 015 Anna Uskova, M.D. Site 020 Hayes Williams, M.D. Site 022 Roger Setzler, M.D. Site 025 J. Daniel Eloy, M.D. Site 027 Stuart Styles, M.D. Site 033 Joseph Gimbel, M.D.
Human Investigational Committee, William Beaumont Hospital, 3811 West 13 Mile Road, Royal Oak, MI 48073 USA, T: 248-551-0662	Site 002 Craig Hartrick, M.D.
CHRISTUS Health IRB, 2707 North Loop West, Suite 5321, Houston, TX 77008, USA, T: 469-282-2577	Site 006 David Leiman, M.D.
Human Subjects Committee, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160 USA, T: 913-588-1240, F: 913-588-5771, humansubjects@kumc.edu	Site 008 John Bracken, M.D.
Institutional Review Board, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195 USA, T: 800-223-2273, F: 216-445-4094	Site 010 Alparslan Turan, M.D.
UCSD Human Research Protections Program, 9500 Gilman Drive, M/C 0052, La Jolla, CA 92093 USA, T: 858-657-5100	Site 011 Brian Ilfeld, M.D.
St. Luke's Roosevelt Hospital IRB, 432 West 58th Street, Antenucci Room 207, New York, NY 10019 USA, T: 212-523-4370, F: 212-523-7442	Site 016 Admir Hadzic, M.D.
Office of Human Research Ethics, 105 Mason Farm Road, CB 7097, Medical School Building 52, Chapel Hill, NC 27599 USA, T: 919-966-3113, ohre.unc.edu	Site 019 David Hardman, M.D.
Sacred Heart Hospital IRB, 5151 North 9th Avenue, Pensacola, FL 32504 USA, T: 850-416-7000, www.sacred-heart.org	Site 024 Eugene Dabezies, M.D.
IRB of the Cleveland Clinic Foundation, 9500 Euclid Avenue, OS-1, Cleveland, OH 44195 USA	Site 028 Sabry Ayad, M.D.
Human Subjects Protection Office, Penn State College of Medicine, 500 University Drive, Hershey, PA 17033 USA, T: 717-531-5687, F: 717-531-3937, www.hmc.psu.edu/irb	Site 030 Sanjib Adhikary, M.D.
Human Subjects Research Office, 1500 NW 12th Avenue, Suite 1002, Miami, FL 33136 USA, T: 305-243-3195, F: 305-243-3326, www.hsro.miami.edu	Site 031 Keith Candiotti, M.D.
Mobile Infirmary Medical Center IRB, 5 Mobile Infirmary Circle, Mobile, AL 36607 USA, T: 251-435-4054, F: 251-435-4669, infirmaryhealth.org	Site 037 Forrest Ringold, M.D.

IEC = independent ethics committee; IRB = institutional review board.